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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09 591,279	06 09 2000	Katayoon Dehesh	15597 01 US	3330

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Calgene L L C
1920 Fifth Street
Davis, CA 95616

EXAMINER

STEADMAN, DAVID J

ART UNIT PAPER NUMBER

1652

DATE MAILED: 03 06 2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/591,279

Examiner

David J. Steadman

Applicant(s)

DEHESH ET AL.

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4-7 and 28-38 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4-7 and 28-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- ☐ Interview Summary (PTO-413) Paper No(s) _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other:

DETAILED ACTION

Application Status

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/28/03 has been entered.

[2] Claims 4-7 and 28-38 are pending in the application.

[3] Receipt of a substitute Declaration and applicants' cancellation of claims 1-3 and 8-27, amendment to claims 4-7, and addition of claims 28-38 in Paper No. 16, filed 11/26/02, is acknowledged.

[4] Applicants' arguments presented in Paper No. 16 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Drawings

[6] Regarding substitute Figure 12, color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

Claim Rejections - 35 USC § 112, Second Paragraph

[7] Claims 30-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 (claims 31-38 dependent therefrom) is indefinite in that it is unclear as to the reference (unengineered) sequence to which the amino acid substitution, insertion or deletion has been incorporated. As such, it is unclear as to the scope of claimed engineered protein sequences. In order to clarify the meaning of the claim, it is suggested that applicants provide a reference sequence to which the substitution, insertion or deletion would be incorporated by, for example, inserting the term "of SEQ ID NO:47" following "acid" in line 4 of claim 30. As written, the claim has been interpreted by the examiner as any modified beta-ketoacyl-acyl carrier protein synthase II (beta-KAS II) protein that preferentially catalyzes the formation of fatty acids having a shorter chain length than fatty acids catalyzed by SEQ ID NO:47.

Claim Rejections - 35 USC § 112, First Paragraph

[8] The written description rejection of claims 4-7 and 28-35 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection as it applied to previously amended claims was fully explained in a previous Office action (see item 4 of Paper No. 12).

Applicants argue the rejection has been overcome by amendment. Applicants' argument is not found persuasive. The structures of the genus of claimed engineered beta-KAS II proteins have not been adequately described in the specification. As stated in a previous Office action, the CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define

Art Unit: 1652

any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of engineered proteins, *the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.*

Furthermore, one of skill in the art would recognize the claimed genus of polypeptides encompasses widely variant structures with substantial variation. Claim 4 is drawn to a beta-KAS II protein having at least one amino acid substitution, insertion, or deletion of SEQ ID NO:47 at the recited positions and having the recited function. Claim 30 is drawn to a beta-KAS II protein having at least one amino acid substitution, insertion, or deletion of any beta-KAS II protein and having the recited function. The disclosed species of mutant beta-KAS II proteins are insufficient to provide a representative number of species for adequate description of the claimed genus. Therefore, the specification does not describe the claimed genus of engineered beta-KAS II proteins such that a skilled artisan would recognize that applicants were in possession of the claimed invention.

[9] The scope of enablement rejection of claims 4-7 and 28-35 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection as it applied to previously amended claims was fully explained in a previous Office action (see item 5 of Paper No. 12).

Applicants argue the rejection has been overcome by amendment. Applicants' argument is not found persuasive. Undue experimentation would be required for a skilled artisan to make the entire scope of claimed beta-KAS II proteins. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). The Factors most relevant to the instant rejection are addressed below:

Art Unit: 1652

- The breadth of the claims: The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of engineered beta-KAS II proteins broadly encompassed by the claims. Claims 4-7, 28, and 29 are so broad as to encompass *any* engineered beta-KAS II protein having *any* amino acid substitution, insertion, or deletion at the recited positions of SEQ ID NO:47 and having the recited function. Claims 30-35 are so broad as to encompass nearly *any* engineered beta-KAS II protein that preferentially catalyzes the formation of fatty acids having a shorter chain length than fatty acids catalyzed by SEQ ID NO:47. In this case, the specification is enabling for the polypeptide of SEQ ID NO:47 with amino acid substitutions at positions 108, 111, 114, 133, 193, and 197 and having altered substrate specificity as compared to SEQ ID NO:47 and optionally wherein long chain fatty acid accumulation is increased or decreased as compared to that of SEQ ID NO:47 or preferentially catalyzing the formation of fatty acids having a shorter chain length than fatty acids catalyzed by SEQ ID NO:47.
- The lack of guidance and working examples: The specification provides guidance in the form of only eight working examples of engineered beta-KAS II proteins that result a decrease in long chain fatty acid accumulation (see Figure 7) and only 7 working examples of engineered beta-KAS II proteins that result in an increase in long chain fatty acids (see Figure 7). These working examples in combination with the other teachings of the specification and prior art fail to provide the necessary guidance for generating the mutants of the beta-KAS II of SEQ ID NO:47 or of any beta-KAS II with an expectation of having the desired activity.
- The relative skill of those in the art: At the time of the invention, neither the skill of those in the art or the guidance provided by the prior art alone or in combination with the teachings of the instant specification was sufficient to predict those mutations that would successfully result in a beta-KAS II protein with the desired activity. Thus, a skilled artisan would be required to test all possible combination of mutations to determine if said combination would result in a beta-KAS II protein with the desired activity.

Art Unit: 1652

- The amount of experimentation: While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. For example, Witowski et al. (*Biochemistry* 38:11643-11650; IDS reference) teach a single mutation in the amino acid sequence of *E. coli* beta-KAS II that results in the conversion of the of the activity of the protein from beta-ketoacyl synthase to a malonyl decarboxylase (see particularly Table 1, page 11647). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.
- The unpredictability of the art: Due to the lack of guidance for engineering any beta-KAS II protein for catalyzing the formation of fatty acids having a shorter chain length than fatty acids catalyzed by SEQ ID NO:47, one of skill in the art would recognize the high degree of unpredictability in obtaining a beta-KAS II protein with the desired activity. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Art Unit: 1652

Conclusion

[10] No claim is in condition for allowance. All claims are rejected.

[11] The examiner requests that applicants provide a copy of all pending claims in the response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for Group 1600 is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

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